CHEST

Relationship of Bisphosphonate Therapy and Atrial Fibrillation/Flutter

Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study

Samir R. Thadani, MD, MEng; Bryan Ristow, MD; Terri Blackwell, MS; Reena Mehra, MD; Katie L. Stone, PhD; Gregory M. Marcus, MD, MAS; Paul D. Varosy, MD; Steven R. Cummings, MD; and Peggy M. Cawthon, PhD; for the Osteoporotic Fractures in Men Study (MrOS) Research Group

BACKGROUND: Prior studies suggested an association between bisphosphonates and atrial fibrillation/flutter (AF) in women. This relationship in men, including those with sleep-disordered breathing (SDB), remains unclear. This study evaluated the relationship between bisphosphonate use and prevalent (nocturnal) and incident (clinically relevant) AF in a population of community-dwelling older men.

METHODS: A total of 2,911 male participants (mean age, 76 years) of the prospective observational Osteoporotic Fractures in Men Study sleep cohort with overnight in-home polysomnography (PSG) constituted the analytic cohort. Nocturnal AF from ECGs during PSG and incident AF events were centrally adjudicated. The association of bisphosphonate use and AF was examined using multivariable-adjusted logistic regression for prevalent AF and Cox proportional hazards regression for incident AF.

RESULTS: A total of 123 (4.2%) men were current bisphosphonate users. Prevalent nocturnal AF was present in 138 participants (4.6%). After multivariable adjustment, there was a significant association between current bisphosphonate use and prevalent AF (OR, 2.33; 95% CI, 1.13-4.79). In the subset of men with moderate to severe SDB, this association was even more pronounced (OR, 3.22; 95% CI, 1.29-8.03). However, the multivariable-adjusted relationship between bisphosphonate use and incident AF did not reach statistical significance (adjusted hazard ratio, 1.53; 95% CI, 0.96-2.45).

CONCLUSIONS: These results support an association between bisphosphonate use and prevalent nocturnal AF in community-dwelling older men. The data further suggest that those with moderate to severe SDB may be a particularly vulnerable group susceptible to bisphosphonate-related AF. Similar associations were not seen for bisphosphonate use and clinically relevant incident AF. CHEST 2016; 149(5):1173-1180

KEY WORDS: atrial fibrillation; bisphosphonates; sleep-disordered breathing

ABBREVIATIONS: AF = atrial fibrillation/flutter; AHI = apnea-hypopnea index; BMD = bone mineral density; HR = hazard ratio; MrOS = Osteoporotic Fractures in Men Study; PASE = Physical Activity Scale for the Elderly; PSG = polysomnography; SDB = sleep-disordered breathing

AFFILIATIONS: From the Division of Cardiology (Dr Thadani), Department of Medicine, Kaiser Permanente, South San Francisco, CA; the Division of Cardiology (Dr Thadani) and the Division of Cardiology, Electrophysiology Section (Dr Marcus), Department of Medicine, University of California, San Francisco, CA; and the Division of Cardiology (Dr Ristow), Department of Medicine, California Pacific Medical Center, San Francisco, CA; the California Pacific Medical Center Research Institute (Ms Blackwell; and Drs Stone, Cummings, and Cawthon), San Francisco, CA; Sleep Disorders Center (Dr Mehra), Neurologic Institute, Cleveland Clinic Lerner College of Medicine, Cleveland, OH; and the VA Eastern Colorado Health Care System; University of Colorado, Denver; and the Colorado Outcomes Research Group (Dr Varosy), Denver, CO.

This work was previously presented at the American College of Cardiology conference in April 2011 in New Orleans, LA.

FUNDING/SUPPORT: The Osteoporotic Fractures in Men Study (MrOS) is supported by National Institutes of Health funding: the

Bisphosphonates, commonly used to treat osteoporosis, have been shown to increase bone mineral density (BMD) and decrease the risk of osteoporotic fractures.[1-6] However, several randomized trials and observational studies have shown an association between bisphosphonate use and development of atrial fibrillation/flutter (AF).

These trials and the meta-analyses of these trials have relied on adverse event reporting, with follow-up from approximately 2 to 4 years.[7-12] Bisphosphonate use was not related to the occurrence of any AF event but was, however, related to the occurrence of serious AF events in some[7,12] but not all[8,10,11] studies.

The results from observational studies are inconsistent.[13-19] Most studies have been retrospective case-control studies using registry or health-care claims data. Some prior studies have been criticized because the populations were older or had increased comorbid burden, which can predispose people to developing AF. Many studies had few AF events. Most studies have been of women.[7,9,10,13,15,18,19] Of those with male participants,[8,11,14,16] only one reported results by sex.[14] These studies lacked a standardized methodology to assess AF, which could result in clinically unrecognized AF and misclassification.

Although the relationship between sleep-disordered breathing (SDB) and AF has been previously described,[20,21] the role of bisphosphonates in modulating this relationship has not been evaluated. We hypothesized that in a community-dwelling population of older men, bisphosphonate use would be associated with both increased prevalence of nocturnal AF observed during overnight polysomnography (PSG) and increased incidence of symptom-based or clinically relevant AF.

Materials and Methods

Participants

Participants were from the Osteoporotic Fractures in Men Study (MrOS), a prospective cohort study of 5,994 community-dwelling men 65 years or older enrolled between 2000 and 2002 at six clinical centers in the United States. Participants needed to be able to walk without assistance and must not have had a bilateral hip replacement.[22,23]

The MrOS Sleep Study, an ancillary study of the MrOS cohort, was conducted between December 2003 and March 2005 and recruited 3,135 MrOS participants for a comprehensive sleep assessment. Men undergoing sleep apnea treatment (eg, positive airway pressure therapy) or receiving nocturnal oxygen therapy were excluded. Of the 2,859 men who did not participate, 349 died before the visit, 39 had terminated the study, 324 were not asked because recruitment goals were met, 150 were ineligible, and 1,997 refused. The 2,859 men who did not participate were similar in age, race, and BMI compared with the 3,135 MrOS Sleep Study participants. Of the 3,135 men, PSG recordings were available for 2,911. Incident AF was adjudicated in 2,861.

All men provided written informed consent. The study was approved by the institutional review board at each site. The committee names and approval numbers are as follows: University of Alabama at Birmingham Institutional Review Board for Human Use, F030725004; Human Research Protection Program at the University of Minnesota, 0307M50161; Stanford University, Protocol ID, 13647; University of Pittsburgh Institutional Review Board, IRB980305; Oregon Health & Science University, Institutional Review Board IRB00001296, CR00020385; University of California, San Diego Human Research Protections Program, 071795; and Sutter Health Institutional Review Board, 348922-9.

Prevalent Nocturnal AF

In-home overnight PSG was completed using unattended, portable units (Safiro; Compumedics Ltd). The data collection method has been previously described.[20] Data quality was excellent, with a failure rate of $< 4\%$ and $> 70\%$ of studies graded as being of excellent or outstanding quality.

ECG-specific software was used to analyze the ECG data collected during PSG (Somté; Compumedics Ltd). Data were scored as supraventricular (including AF as a subcategory), ventricular ectopic, or normal sinus beats. The data were manually reviewed by a polysomnologist with ECG training, with arbitration by a board-certified critical care physician (R.M.) for any uncertainty in event categorization. The intraclass correlation coefficients for this reviewer and the physician for coding arrhythmia in a random sample of 20 PSGs were 0.98 to 0.99.[21] All PSG recordings demonstrating nocturnal AF were confirmed by the physician. Any questionable categorization of arrhythmias was referred to a cardiologist for further arbitration. Prevalent nocturnal AF was considered the presence of any duration of AF during sleep observed during the course of the overnight sleep study (mean $\pm$ SD, 5.9 $\pm$ 1.2 hours).

National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Center for Advancing Translational Sciences, and National Institutes of Health Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128. The National Heart, Lung, and Blood Institute provides funding for the MrOS Sleep ancillary study "Outcomes of Sleep Disorders in Older Men" under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839.

CORRESPONDENCE TO: Samir R. Thadani, MD, Kaiser Permanente, 1200 El Camino Real, South San Francisco, CA 94080; e-mail: samir.r.thadani@kp.org

DOI: http://dx.doi.org/10.1016/j.chest.2015.11.022